



HOW LATE IS TOO LATE TO RECANALIZE CAROTID AND INTRACRANIAL THROMBOSIS AFTER STROKE?







The earlier the better

The longer therapy is delayed, the lesser the chance that it will be successful.



Time Is Brain: The Stroke Theory of Relativity

Camilo R. Gomez, MD, MBA*,†

The effect of time can vary greatly among patients

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The spatial pattern of cerebral blood flow (CBF) reduction following middle cerebral artery (MCA) occlusion, demonstrating a gradient from ischaemic core (red) through to penumbra and oligaemia (blue) to normally perfused cortex (grey). Values indicate approximate CBF in ml 100 g/min

ISCHAEMIC BRAIN INJURY RESULTS FROM A COMPLEX SEQUENCE OF PATHOPHYSIOLOGICAL EVENTS EVOLVING OVER TIME AND SPACE



Pathophysiology of ischaemic stroke

PENUMBRA - MRI



Diffusion Weighted Image Yellow area → CORE

Perfusion Weighted Image Red area → hypoperfused tissue

Blue area → MISMATCH DWI-PWI = penumbra

PENUMBRA – perfusion CT



Pathophysiological Topography of Acute Ischemia by Combined Diffusion-Weighted and Perfusion MRI

"Penumbra patterns" are likely to be found in the early hours after stroke onset but may also be seen up to 24 hours.



Penumbra



VERY DIFFERENT

MISMATCH PROFILES

In TWO PATIENTS

No Mismatch Profile

5 hr 15 min after stroke onset:





Timing for thrombolysis



0.30).

TISSUE PLASMINOGEN ACTIVATOR FOR ACUTE ISCHEMIC STROKE

THE NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE rt-PA STROKE STUDY GROUP*

As compared with patients given placebo, patients treated with t-PA were at least 30 percent more likely to have minimal or no disability. Symptomatic intracerebral hemorrhage within 36 hours after the onset of stroke occurred in 6.4 percent of patients given t-PA but only 0.6 percent of patients given placebo (P 0.001). Mortality at three months was 17 percent in the t-PA group and 21 percent in the placebo group (P

Conclusions

Despite an increased incidence of symptomatic intracerebral hemorrhage, treatment with intravenous t-PA within three hours of the onset of ischemic stroke improved clinical outcome at three months.

Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials THE LANCET, 2004

	Treatment n		Odds ratio (95% CI)*		
			Adjusted	Unadjusted	
Interval (m	in)				
0-90	rt-PA	161	2.81 (1.75-4.50)	1.96 (1.30-2.95)	
	Placebo	150			
91-180	rt-PA	302	1.55 (1.12-2.15)	1.65 (1.23-2.22)	
	Placebo	315			
181-270	rt-PA	390	1.40 (1.05-1.85)	1.34 (1.04-1.72)	
	Placebo	411			
271-360	rt-PA	538	1.15 (0.90-1.47)	1.04 (0.84-1.29)	
l	Placebo	508			

Odds ratio for a favourable outcome at 3 months after stroke

The sooner that rt-PA is given to stroke patients, the greater the benefit, especially if started within 90 min. **Our results suggest a potential benefit beyond 3 h**, but this potential might come with some risks.



Timing for thrombolysis

Thrombolysis with Alteplase 3 to 4.5 Hours after Acute Ischemic Stroke N Engl J Med 2008



Conclusions

As compared with placebo, intravenous alteplase administered between 3 and 4.5 hours after the onset of symptoms significantly improved clinical outcomes in patients with acute ischemic stroke; alteplase was more frequently associated with symptomatic intracranial hemorrhage Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials

Emberson et al

Lancet 2014; 384: 1929–35



Interpretation Irrespective of age or stroke severity, and despite an increased risk of fatal intracranial haemorrhage during the first few days after treatment, alteplase significantly improves the overall odds of a good stroke outcome when delivered within 4.5 h of stroke onset, with earlier treatment associated with bigger proportional benefits.

ENDOVASCULAR TREATMENT FOR LARGE VESSEL OCCLUSION STROKE



2015

2018



Within 6 hours

The NEW ENGLAND JOURNAL of MEDICINE



A Randomized Trial of Intraarterial Treatment for Acute Ischemic Stroke Thrombectomy within 8 Hours after Symptom Onset in Ischemic Stroke Stent-Retriever Thrombectomy after Intravenous t-PA vs. t-PA Alone in Stroke Endovascular Therapy for Ischemic Stroke with Perfusion-Imaging Selection Randomized Assessment of Rapid

Endovascular Treatment of Ischemic Stroke

REVASCAT

MR CLEAN

SWIFT PRIME

EXTEND-IA

ESCAPE

Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials

	Intervention population	Control population	Risk difference (%)
mRS score reduction (shift analysis; primary outcome)*			
mRS score 0–1 at 90 days	26-9% (170/633)	12·9% (83/645)	14-0
mRS score 0-2 at 90 days	46-0% (291/633)	26-5% (171/645)	19-5
NIHSS score 0–2 at 24 h	21.0% (129/615)	8-3% (52/630)	12-7
Early neurological recovery at 24 h	50-2% (309/616)	21·2% (134/633)	29-0



Interpretation Endovascular thrombectomy is of benefit to most patients with acute ischaemic stroke caused by occlusion of the proximal anterior circulation, irrespective of patient characteristics or geographical location. These findings will have global implications on structuring systems of care to provide timely treatment to patients with acute ischaemic stroke due to large vessel occlusion.

JAMA | Original Investigation

Time to Treatment With Endovascular Thrombectomy and Outcomes From Ischemic Stroke: A Meta-analysis



CONCLUSIONS AND RELEVANCE In this individual patient data meta-analysis of patients with large-vessel ischemic stroke, earlier treatment with endovascular thrombectomy + medical therapy compared with medical therapy alone was associated with lower degrees of disability at 3 months. Benefit became nonsignificant after 7.3 hours.

Disability free-survival at three months







2015

2018



DAWN DEFUSE III

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Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct

DAWN

Thrombectomy for Stroke at 6 to 16 Hours DEFUSE with Selection by Perfusion Imaging

Late Window Paradox

Stroke. 2018



REAL-WORLD THROMBECTOMY BEYOND 6 HOURS FROM ONSET OF ACUTE ISCHEMIC STROKE DUE TO LARGE VESSEL OCCLUSION

I <u>Casetta</u>¹, G. Pracucci², V. Saia³, A. Saletti¹, S. Nappini², L. Castellan⁴, E. Cagliari⁵, N.P. Nuzzi⁶, S. Vallone⁷, R. Padolecchia³, D. Konda⁸, P. Amistá⁹, E. Puglielli¹⁰, A. Giorgianni¹¹, D. Toni⁸, S. Mangiafico² on behalf of the Italian Registry of Endovascular Treatment for Acute Stroke Ferrara¹, Firenze², Pietra Ligure³, Genova⁴, Mestre⁵, Rozzano⁶, Modena⁷, Roma⁸, Rovigo⁹, Teramo¹⁰, Varese¹¹, Italy

327 pz treated beyond 6 hours (6-24)

Functional independence (mRS 0-2) was achieved at the 90-day follow-up by 41.3 % of cases.

The proportion of stroke patients with complete recovery or minimal disability at 3 months (mRS =0-1) was 26.9%. Three-month case fatality rate was 17.1 %. Symptomatic intracranial hemorrhage occurred in 22 patients (6.7%).

The main finding of our real-world study is that MRI or CTP imaging based endovascular therapy in patients with acute ischemic stroke treated beyond 6 hours from onset can be performed with a safety profile that is similar to that observed in patients treated earlier.

Patients receiving ET beyond 6 hours achieved outcomes comparable to DAWN and DEFUSE-3 eligible patients. These data indicate that a larger population of patients could benefit from ET in an expanded time window, in real-world settings.

Thrombolysis Guided by Perfusion Imaging up to 9 Hours N Engl J Med, May 9, 2019. after Onset of Stroke



CONCLUSIONS^{Percentage of Patients}

Among patients who had ischemic stroke and salvageable brain tissue, the use of alteplase between 4.5 and 9.0 hours after stroke onset or at the time the patient awoke with stroke symptoms resulted in a higher percentage of patients with no or minor neurologic deficits than the use of placebo. There were more cases of symptomatic cerebral hemorrhage in the alteplase group than in the placebo group.

Extending thrombolysis to 4.5–9 h and wake-up stroke using perfusion imaging: a systematic review and meta-analysis of individual patient data May 22, 2019

Bruce C V Campbell^{*}, Henry Ma^{*}, Peter A Ringleb^{*}, Mark W Parsons, Leonid Churilov, Martin Bendszus, Christopher R Levi, Chung Hsu, Timothy J Kleinig, Marc Fatar, Didier Leys, Carlos Molina, Tissa Wijeratne, Sami Curtze, Helen M Dewey, P Alan Barber, Kenneth S Butcher, Deidre A De Silva, Christopher F Bladin, Nawaf Yassi, Johannes A R Pfaff, Gagan Sharma, Andrew Bivard, Patricia M Desmond, Stefan Schwab, Peter D Schellinger, Bernard Yan, Peter J Mitchell, Joaquín Serena, Danilo Toni, Vincent Thijs, Werner Hacke[†], Stephen M Davis[†], Geoffrey A Donnan[†], on behalf of the EXTEND, ECASS-4, and EPITHET Investigators[‡]

> We did a meta-analysis of individual patient data to test the hypothesis that intravenous alteplase improves functional outcomes compared with placebo in patients with ischaemic stroke 4.5-9 h after onset or wake-up stroke who were imaged with CT perfusion or perfusiondiffusion MRI.

	Placebo (n=201)	Alteplase (n=213)	Odds ratio* (95% CI)	p value
Primary outcome				
Excellent functional outcome (mRS score 0–1) at 3 months	58/199 (29%)	76/211 (36%)	1.86 (1.15-2.99)	0.01
Secondary outcomes				
Functional improvement in mRS score at 3 months†	NA	NA	1.60 (1.12-2.27)	0.009
Functional independence (mRS score 0–2) at 3 months	87/199 (44%)	103/211 (49%)	1.74 (1.08-2.81)	0.02
Early neurological improvement at 72 h‡	31/197 (16%)	58/206 (28%)	2.54 (1.51-4.27)	<0.0001
Safety outcomes				
Death at 3 months	18/201 (9%)	29/213 (14%)	1.55 (0.81-2.97)	0.19
Symptomatic intracerebral haemorrhage§	1/201 (<1%)	10/213 (5%)	9.70 (1.23-76.55)	0.03

Interpretation Patients with ischaemic stroke 4.5–9 h from stroke onset or wake-up stroke with salvageable brain tissue who were treated with alteplase achieved better functional outcomes than did patients given placebo. The rate of symptomatic intracerebral haemorrhage was higher with alteplase, but this increase did not negate the overall net benefit of thrombolysis.

Guidelines of the European Stroke Organization



In patients with ischaemic stroke of 4.5 to 9 hours duration, and with CT or MRI perfusion/core penumbra mismatch, and for whom mechanical thrombectomy is not planned, we suggest alteplase over no alteplase

In patients with...., and without advanced imaging, we recommend no alteplase over alteplase

SVN Stroke and Vascular Neurology **Tissue window, not the time window, will guide acute stroke treatment**